



Probiotics and asthma, new insight

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Over the past decades, an increase in the incidence of allergic diseases and asthma has been observed in pediatric patients, in particular in the industrial countries. Many theories have been suggested to explain this phenomenon and the most plausible hypothesis is the "hygiene hypothesis", elaborated by Strachan in 1989 (1). According to the "hygiene hypothesis", the immune system lack of exposure to microbial agents in the early years of life, increases the risk of allergic diseases (1). Hence children who live in countries with the best hygienic-sanitary conditions have a predisposition to allergies, because of the reduced environmental antigen stimulation. In these patients the physiological immune system "switch" Th2-Th1 turns out to be damaged with a lack of immunological tolerance. Another theory, the "microflora hypothesis", said that the overuse of antibiotics and the changes in the diet typical of the industrial countries, have disrupted the normal microbiota-mediated mechanisms of immunological tolerance in the mucosa, which has led to an increase in the incidence of allergic diseases (2). A lot of studies indicate that the GI microbiota is different in atopic vs. non-atopic individuals and in industrialized vs. developing countries (3, 4). Although experimental data have shown that the endogenous microbiota plays a significant role in shaping the development of the immune system (5-7). The probiotics restore the normal intestinal permeability and gut microecology, improve the intestinal immunologic barrier function, reduce the intestinal inflammatory response and generation of proinflammatory cytokines characteristic of local and systemic allergic inflammation (8). In clinical trials probiotics appear to be useful for the treatment of various clinical conditions such as food allergy (9) and atopic dermatitis (10), and even in primary prevention of atopy (11, 12). Recently it has been hypothesized that oral administration of specific live probiotic strains may have therapeutic potential in the treatment of allergic airway disease (13, 14). Giovannini et al (15) selected 187 children (range 2-5 years old), affected by allergic asthma and/or allergic rhinitis. Patients were randomized to use fermented milk containing *L. casei* DN-114 001, *L. bulgaris* and *Streptococcus thermophilus* or placebo. The results of this study shown no beneficial effects on asthma symptoms and any immunologic in both the groups. On the contrary, in the patients suffering from allergic rhinitis, the episodes number was slightly lower compared to the placebo group. Wheeler et al. (16) made a clinical study to evaluate the possible beneficial effect of the treatment with yoghurt containing *L. acidophilus* in 15 adult patients (average age 33 years old) suffering from moderate asthma. Even in this study, this treatment did not show significant clinical effects neither on the symptomatology nor on the respiratory function tests nor in the immunological parameters (eosinophilia, total IgE or the IL-2, IL-4, and IFN γ production by the lymphoid cells). Two recent studies that confirm the effectiveness of the allergic asthmatic disease treatment both with the probiotic have been published recently. Van de Pol et al (17) evaluated in a randomized double-blind placebo controlled study the effectiveness of a symbiotic (90% short-chain galacto-oligosaccharides, 10% long-chain fructo-oligosaccharides: Immunofortis® and *Bifidobacterium breve* M-16V), in 29 adult patients suffering from allergic asthma and HDM allergy. At the beginning of the study and at the end of the treatment a bronchial challenge with HDM was done, spirometry and PC20 methacholine test to assess pulmonary function. To evaluate the bronchial inflammation the ECP and the myeloperoxidase (MPO) levels were measured in the sputum. The results showed that Th2 cytokines as IL-4, IL-5 and IL-13 levels were lower in the treated group compared to the placebo group. Instead there were no significant differences in the IL-10, IL-12 and IFN- γ production between the 2 groups. In the study of Yue-Sheng Chen et al., (18) 105 children (range 6-12 years old), affected by mild persistent asthma and allergic rhinitis (AR) were treated with the *L. gasseri* A5 or placebo for 2 months. The results showed a significant improvements in symptoms and in the FEV1, FVC, FEV1/FVC (%) and MEF 25-75 values in the probiotic group. Furthermore there was a significant reduction in the TNF- α , IFN- γ , IL-12 and IL-13 production by the PBMCs in the patients treated with probiotics. An other important aspect is that even this study, made by Yue-Sheng Chen et al., was made on children suffering from allergic asthma. This is an important aspect to be considered because often in the international reference literature the patients do not suffer from allergic asthma or it is not even specified if they have studied the probiotics effects on patients suffering or not from allergic asthma. We have to remember that there are at least 3 well-known hypothesis to explain the probiotics antiallergic effects (19): probiotics could modify the Th2 cytokines profile in atopic conditions because of their Th1-adjuvant effect (20, 21); probiotics could induce the proliferation of a specific subpopulation of Treg, such as Th3 and Th1 and of the natural Treg, suppressing the inflammatory response induced by the allergens (22-24), and finally the last theory says that the probiotics could interact with the cells containing the antigen, like the macrophages and the dendritic cells (DC) that are in the mucous membrane of the gastrointestinal tract determining, this way, a systemic immunologic tolerance. (24-27). The authors of the previous study think that, having not found significant differences in the Total IgE serum levels and in the allergenic sensitization level before and after the probiotic treatment and having not found a significant increase in the correlated Th1 cytokines, like INF- γ and IL-12, in the patients treated with the probiotic, these results, according to them, exclude the possibility that the probiotics work as Th1 adjuvant to balance the Th2 cytokines predominant production in atopic children. On the other hand, the IL-10 cytokine production, produced above all by the inducible Treg, turned out to be reduced instead that increased after the probiotic treatment. Furthermore they noticed that the CD4+CD25highFoxp3+ lymphocytes T (natural Treg) percentage among the PBMC, before and after the treatment with the probiotic, was not significantly different, even if the natural Treg function was improved after the treatment. This last effect could be due to the lower TNF- α production by the PBMC in the treated patients. Therefore, according to these authors, it is unlikely that the probiotics are able to induce the natural or inducible Treg production in the treated patients with the purpose of suppressing the airways allergen-induced inflammation in the asthma and in the AR. The same authors think that the probiotics immunomodulating effect is most performed through their ability to improve the DC activity which facilitates, in the end, the Th1 differentiation. The mechanism of this modulation is still unknown. Nevertheless it has been demonstrated that the lactobacillus cell wall contains immunomodulatory components like some particles of cell surface and the peptidoglycan which can have a very important role in the activation of the immunocompetent cells at the intestinal level. (28). For example, it was demonstrated that the *Lactobacillus* spp. can bind the specific C-type lectin, which is an intercellular adhesion particle of the DC (3-grabbing nonintegrin) or the 2, 4 and 9 toll-like receptors (TLRs) (29) which are the first component of the DC monocytes to lead the Treg cells development that produce an increase in the IL-10 levels, whose cytokine is able to inhibit the T cells proliferation. (30, 31, 24). In conclusion, the data on the real effectiveness of the probiotics in the treatment of the asthmatic disease are still scanty and above all very conflicting. Moreover, the enormous study heterogeneity in the reference literature, about the strains used, the therapy length and doses, does not permit an univocal interpretation. Certainly the main difficulty is the treatment administration timing comprehension compared to the moment in which there is the allergen-specific sensitization in the patient, because some people think that the best effectiveness of the probiotic can be had with its use before and after the allergen-specific sensitization, but the clinical trials that used this approach had very unsatisfying results. As already said, the probiotics effects are strain-specific so it is legitimate to think that were those specific tested probiotics to be unsuitable for the allergic asthma treatment.

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